AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1. (currently amended) A compound of formula I

$$A \xrightarrow{S} R^1$$

$$R^1$$

$$R^2$$

$$R^3$$

or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one of R⁴or R³ is a pyrimidine;

R¹, R², R³, R⁴ and R⁵ are each independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, cyano, nitro, cycloalkyl, carboxaldehyde, and a group of formula II defined as

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and wherein at least one of R¹ or R³ is a pyrimidine;

subject to the proviso that one or more than one of R¹ or R³ is a group of formula II as defined above;

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wherein-D, B, Y and Z at each occurrence are <u>each</u> independently selected from the group consisting of -CR⁶=, -CR⁷R⁸-, -C(O)-, -O-, -SO₂-, -S-, -N=, and -NR⁹-;

n is an integer of zero to three;

R⁶, R⁷, R⁸ and R⁹, at each occurrence- are <u>each</u> independently selected from the group consisting of hydrogen, alkyl, carboxy, hydroxyalkyl,

alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl and carboxyalkyl; and

- R¹⁰ and R¹¹ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, alkoxyarbonylalkyl, carboxyalkyl, hydroxyalkyl, heterocyclylalkyl and heterocyclylamino; or
- R¹⁰ and R¹¹ are taken together with N to form a three to seven membered unsubstituted heterocyclyl-ring, or a three to seven membered substituted heterocyclyl ring, substituted with one or more than one substituent R¹³, wherein R¹³, at each occurrence- is independently selected from the group consisting of alkyl, alkylene, alkoxy, alkoxyalkyl, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclylalkylaminocarbonyl, hydroxy, hydroxyalkyl, hydroxyalkoxyalkyl, carboxy, carboxyalkyl, carboxycarbonyl, carboxaldehyde, alkoxycarbonyl, arylalkoxycarbonyl, aminoalkyl, aminoalkanoyl, aminocarbonyl, carboxamido, alkoxycarbonylalkyl, carboxamidoalkyl, cyano, tetrazolyl, alkanoyl, hydroxyalkanoyl, alkanoyloxy, alkanoylamino, alkanoyloxyalkyl, alkanoylaminoalkyl,

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sulfonate, alkylsulfonyl, alkylsulfonylaminocarbonyl, arylsulfonylaminocarbonyl and heterocyclylsulfonylaminocarbonyl; wherein-A is an unsubstituted aryl group, an unsubstituted heterocyclyl group, a substituted aryl group, or a substituted heterocyclyl group, substituted with one or more than one substituent R¹², wherein R¹², at each occurrence, is independently selected from the group consisting of halogen, alkyl, aryl, haloalkyl, hydroxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxyalkoxy, hydroxyalkyl, aminocarbonyl, alkyl(alkoxycarbonylalkyl) aminoalkyl, heterocyclyl, heterocyclylalkyl, carboxaldehyde, carboxaldehyde hydrazone, carboxamido, alkoxycarbonylalkyl, carboxy, carboxyalkyl, carboxyalkoxy, hydroxyalkylaminocarbonyl, cyano, amino, heterocyclylalkylamino, carboxythioalkoxy, carboxycycloalkoxy, thioalkoxy, carboxyalkylamino, trans-cinnamyl and heterocyclylalkylaminocarbonyl; and

- wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are unsubstituted or substituted with one or more than one electron donating or electron withdrawing group
- wherein the heterocyclyl is chosen from <u>3-,</u> 4-, 5-, 6- and 7-membered rings containing 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; the 4- and 5-membered rings have zero to two double bonds and the 6- and 7-membered rings have zero to three double bonds, the heterocycle heterocyclyl being optionally substituted with alkyl, halogen, hydroxy or alkoxy substituents,

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further wherein the heterocyclyl optionally comprises a group chosen from:

- (i) bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, and another monocyclic heterocyclic ring;
- (ii) bridged bicyclic groups where a monocyclic heterocyclic group is bridged by an alkylene group optionally selected from

$$\frac{H}{A}$$
, $\frac{1}{A}$, $\frac{1}{A}$, and

(iii) compounds of the formula

where X* and Z* are each

independently selected from -CH₂-, -CH₂NH-, -CH₂O-, -NH- and -O-, with the proviso that at least one of X* and Z* is not -CH₂-, and Y* is selected from -C(O)- and -($C(R")_2$)_v -, where R" is hydrogen or alkyl of one to four carbons, and v is 1-3.

2. (previously presented) A compound according to claim 1 wherein R³ is the group of formula II

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wherein R^{10} , R^{11} , D, B, Y, Z, and n are defined as in claim 1; and R^{1} is defined as in claim 1 with the proviso that if R^{3} does not define a pyrimidine, then R^{1} is a pyrimidine.

3. (previously presented) A compound according to claim 1 of formula III

$$(R^{12})_p$$
 R^5 R^4 R^2 $NR^{10}R^{11}$ R^5 R^4 R^4 R^5 R^4 R^5 R^6

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wherein R^1 , R^2 , R^4 , R^5 , R^{10} , R^{11} , R^{12} , D, B, Y, Z, and n are defined as in claim 1; and p is an integer of zero to five.

4. (previously presented) A compound according to claim 3 wherein p is one;

R⁴ and R⁵ are hydrogen;

R¹² is selected from the group consisting of halogen, alkyl, alkoxy, carboxyalkoxy, carboxyalkyl and heterocyclyl;

R¹⁰ and R¹¹ are taken together with N to form a three to seven membered unsubstituted heterocyclyl ring, or a three to seven membered substituted heterocyclyl ring, substituted with one or more than one subsituent R¹³, wherein R¹³ is defined as in claim 1, and wherein said substituted

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heterocyclyl, or unsubstituted heterocyclyl ring is selected from the group consisting of piperidine, piperazine, morpholine, pyrrolidine, and azetidine; and

- wherein R¹⁰, R¹¹, R¹² and R¹³ are unsubstituted or substituted with at least one electron donating or electron withdrawing group.
- 5. (previously presented) A compound according to claim 1 of formula IV

$$(R^{12})_p$$
 R^2 $NR^{10}R^{11}$

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wherein D and B are each independently selected from the group consisting of -N= and -CR⁶=;

R¹ is selected from the group consisting of hydrogen, halogen and haloalkyl, with the proviso that if R³ does not define a pyrimidine, then R¹ is a pyrimidine; R² is selected from the group consisting of hydrogen, halogen and haloalkyl; R¹⁰ and R¹¹ are defined as in claim 1:

- R¹², at each occurrence, is independently selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, carboxyalkoxy, carboxyalkyl and heterocyclyl, wherein R¹² is unsubstituted or substituted with at least one electron donating group or electron withdrawing group; and p is an integer of zero to five.
- 6. (previously presented) A compound according to claim 5 wherein p is one; and

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R¹⁰ and R¹¹ are taken together with N to form a three to seven membered substituted heterocyclyl ring, or a three to seven membered unsubstituted heterocyclyl ring, substituted with one or more substituents R¹³, wherein R¹³ is defined as in claim 1, and wherein said substituted heterocyclyl ring, or unsubstituted heterocyclyl ring is selected from the group consisting of piperidine, piperazine, morpholine, pyrrolidine, and azetidine.

7. (previously presented) A compound according to claim 1, selected from the group consisting of 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4yl)-piperidine-3-carboxylic acid, 4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethylphenyl)-6-(3-(2H-tetrazol-5-yl)-piperidin-1-yl)-pyrimidine, 4-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(4-(2H-tetrazol-5-yl)-piperidin-1-yl)pyrimidine, (1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4yl)-piperidin-3-yl)-methanol, 2-(1-(6-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethylphenyl)-pyrimidin-4-yl)-piperidin-4-yl)-ethanol, 4-(6-(4-(2-isopropyl-phenylsulfanyl)-3trifluoromethyl-phenyl)-pyrimidin-4-yl)-morpholine, 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-vl)-piperidin-4-ol, 4-(6-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-2.5-dimethyl-morpholine, 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3carboxylic acid amide, 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)pyrimidin-4-yl)-piperidine-4-carboxylic acid amide, N-Ethyl-N-1-(6-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-pyrrolidin-3-yl)-acetamide, 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3carboxylic acid ethyl ester, 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-

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phenyl)-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester, 4-(6-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperazine-1-carboxylic acid ethyl ester, 4-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)piperazin-1-yl-acetic acid ethyl ester, (3-imidazol-1-yl-propyl)-(6-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-amine, 1-(6-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-4-carboxylic acid, 4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3carboxylic acid, 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3-carboxylic acid diethyl amide, N-1-(6-(4-(2-isopropyl-phenylsulfanyl)-3trifluoromethyl-phenyl)-pyrimidin-4-yl)-pyrrolidin-3-yl)-acetamide, 4-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(2-methoxymethyl-pyrrolidin-1-yl)-pyrimidine, 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-pyrrolidin-3ol, (1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)pyrrolidin-3-yl)-carbamic acid tert-butyl ester, isopropyl-(6-(4-(2-isopropylphenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-methyl amine, and ethyl-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-methyl-amine.

- 8. (previously presented) A composition comprising:
 - a compound according to claim 1
 - and a pharmaceutically acceptable carrier.
- 9. (previously presented) A method of inhibiting inflammation or suppressing immune response in a mammal comprising administering to said mammal a therapeutic amount of a compound according to claim 1.
- 10. (previously presented) A compound according to claim 1 wherein A is

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- (i) an unsubstituted or substituted aryl group, substituted by one or more than one substituent R¹², wherein R¹² is defined as in claim 1, or
 - (ii) an unsubstituted or substituted heterocyclyl group of the formula

wherein

R¹² and is defined as in claim 1;

p is an integer of 0 to 5;

X* and Z* are each independently selected from the group consisting of -CH₂-, -CH₂NH-, -CH₂O-, -NH-, and -O-, with the proviso that at least one of X* and Z* is not -CH₂-; and

Y* is -(C(R")₂)_v-, wherein

R" is hydrogen or alkyl; and

v is 1, 2, or 3.

- 11. (previously presented) A compound according to claim 1 or 10 wherein A is an unsubstituted or substituted aryl group, wherein the aryl group is
- (I) a mono- or a bicyclic carbocyclic ring system having one or two aromatic rings, or
- (ii) a mono- or a bicyclic carbocyclic ring system having one or two aromatic rings,

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wherein one or more than one of the aromatic rings is fused to a ring selected from the group consisting of cyclohexane, cyclohexene, cyclopentane, and cyclopentene.

12. (previously presented) A compound according to claim 1 wherein A is an unsubstituted or substituted aryl group of the formula

wherein R¹² is defined as in claim 1; and p is an integer of 0 to 5.

13. (previously presented) A compound according to claim 1 wherein

Y is
$$-CR^6$$
= or $-N$ =,

n is zero or one.

14. (previously presented) A compound according to claim 1 wherein R³ is selected from the group consisting of

 R^1 is defined as in claim 1 with the proviso that if R^3 does not define a pyrimidine, then R^1 is a pyrimidine.

15. (previously presented) A compound according to claim 1 wherein,

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B is -O- or -S-;

Y is -N=; and

n is zero.

16. (previously presented) A compound according to claim 1 wherein

D is $-CR^6 = or -N=$;

B is -N=;

Y is CR⁶=; and

n is 1.

17. (currently amended) A compound according to claim 1 wherein

R¹ is selected from the group consisting of hydrogen, halogen, alkyl, and nitro,

and
$$(Z)^n$$
 $NR^{10}R^{11}$ wherein

wherein R¹⁰, R¹¹, D, B, Y, Z, and n are defined

as in claim 1, with the proviso that if R^3 does not define a pyrimidine, then R^1 is a pyrimidine;

R² is selected from the group consisting of hydrogen, halogen, alkyl, and nitro;

 $\ensuremath{\mbox{R}^4}$ and $\ensuremath{\mbox{R}^5}$ are each independently selected from the group consisting of

hydrogen and alkyl; and

R³ is

wherein

D is $-CR^6 = \text{ or } -N =$,

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18. (previously presented) A compound according to claim 1 wherein
R¹ and R² are each independently selected from the group consisting of hydrogen, halogen, and haloalkyl;

R³ is a pyrimidine; and

R⁴ and R⁵ are each independently hydrogen.

(currently amended) A compound according to claim 1 wherein
 R¹ is selected from the group consisting of hydrogen, halogen, and haloalkyl,

<u>as in claim 1,</u> with the proviso that if \mathbb{R}^3 does not define a pyrimidine, then \mathbb{R}^1 is a pyrimidine;

 R^2 is selected from the group consisting of hydrogen, halogen, and haloalkyl; R^4 and R^5 are each independently hydrogen; and R^3 is

wherein

D is
$$-CR^6 = or -N =$$
,

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B is -S-, -O-, -CR⁶= or -N=, Y is -CR⁶= or -N=, Z is -CR⁶= or -N=; and n is zero or one.

20. (currently amended) A compound according to claim 1 wherein

R¹ is selected from the group consisting of hydrogen, halogen, and haloalkyl,

as in claim 1, with the proviso that if R^3 does not define a pyrimidine, then R^1 is a pyrimidine;

R² is selected from the group consisting of hydrogen, chloro, and trifluoromethyl;

R⁴ and R⁵ are each independently hydrogen; and

R³ is selected from the group consisting of

$$R^{10}$$
 R^{10} R^{10} R^{10} R^{10} , and R^{11} , and R^{11}

- 21. (previously presented) A compound according to claim 1 wherein R⁶ is hydrogen.
- 22. (previously presented) A compound according to claim 1 wherein

R¹ is selected from the group consisting of hydrogen, halogen and haloalkyl,

R² is selected from the group consisting of hydrogen and halogen,

R³ is a pyrimidine, and

R⁴ and R⁵ are each hydrogen.

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23. (previously presented) A compound according to claim 22 wherein

R¹ is trifluoromethyl,

R² is hydrogen, and

R³ is a pyrimidine.

- 24. (previously presented) A compound according to claim 22 wherein R¹ and R² are each chloro, and R³ is a pyrimidine.
- 25. (previously presented) A compound according to claim 1 which has an IC₅₀ of less than 20 μ M when tested in one or both of
 - (i) an ICAM-1/LFA-1 Biochemical Interaction Assay, or
 - (ii) an ICAM-1/JY-8 Cell Adhesion Assay
- 26. (previously presented) A method for ameliorating a pathology in a mammal arising from the interaction of LFA-1 with ICAM-1 or ICAM-3 comprising administering to said mammal a therapeutic amount of a compound according to claim 1.
- 27. (previously presented) A method according to claim 26 wherein the pathology is selected from an inflammatory disease, an autoimmune disease, tumor metastasis, allograft rejection and reperfusion injury.

REMARKS

I. Status of the Claims

Claims 1-27 are pending in the application. Claims 1, 17, 19, and 20 have been amended. Claim 15 is withdrawn from consideration.

Claim 1 has been amended to require that R¹ and R³ be selected from the recited group. In light of this amendment to claim 1, dependent claims 17, 19, and 20 have

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been amended to expand the recited group for R¹ to include the compound of formula II.

These amendments are also consistent with the existing provisos in claims 17, 19, and

20 that R¹ be a pyrimidine if R³ does not define a pyrimidine.

Claim 1 has also been amended to define heterocyclyl as chosen from <u>3-</u>, 4-, 5-, 6- and 7-membered rings to render this definition consistent with the definition of unsubstituted and substituted heterocyclyl for R¹⁰ and R¹¹. Other minor amendments have been made for the purposes of clarity.

No new matter has been added by these amendments, nor do these amendments raise new issues or necessitate the undertaking of any additional search of the art by the Examiner. Accordingly, Applicants respectfully request further examination of the claims.

The Examiner recommends that claim 15 be deleted, asserting that it is drawn to a non-elected invention. *Final Office Action* at p. 2. Applicants respectfully disagree. Dependent claim 15 can define a non-pyrimidine so long as the compound of formula I includes a pyrimidine at the R¹ or R³ position, a proviso that is explicitly recited in independent claim 1. Accordingly, Applicants respectfully request examination of claim 15.

II. Objection to the claims

The Examiner has objected to claim 13 as allegedly "drawn to multiple inventions for reasons set forth in the restriction requirement." *Final Office Action* at p. 2. The Examiner further states that "only one of R¹ or R³ is permitted to be a pyrimidine ring." *Id.* at 3.

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Applicants respectfully disagree. Both R¹ or R³ can be a pyrimidine so long as at least one of R¹ or R³ defines a group of formula II, which can be a pyrimidine. Stated otherwise, R¹ and/or R³ can be both a group of formula II and a pyrimidine. Claim 13 further limits the group of formula II such that D, B, Y, and Z are chosen from specified radicals. Claim 13 can read on the elected invention whether or not the group of formula II defines a pyrimidine. For example, if claim 13 defines a group of formula II that is not a pyrimidine and this group is assigned as R³, then R¹ is necessarily a pyrimidine (and vice versa). Thus, claim 13 does not have to define a pyrimidine to read on the elected invention by virtue of the proviso in claim 1 requiring that at least one of R¹ or R³ be a pyrimidine.

Finally, Applicants respectfully disagree that "only one of R¹ or R³ is a pyrimidine as was done in claim 20." *Id.* In claim 20, the R³ is selected from four substituents. The third substituent is a pyrimidine. Thus, if R³ is not a pyrimidine, the proviso of claim 20 requires that R1 be a pyrimidine. If R³ is a pyrimidine, the proviso does not exclude R¹ from being a pyrimidine. Moreover, claim 20 has been amended to clarify this existing proviso to allow R¹ to be selected from the group of formula II, which can define a pyrimidine.

Accordingly, it is respectfully requested that the objection to claim 13 be withdrawn.

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III. Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-14 and 16-27 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. *Final Office Action* at pp. 3-4. Applicants respectfully traverse this rejection.

The Examiner believes that the proviso "one or more than one of R^1 or R^3 is a group of formula II as defined above" is not clear. *Id.* at p. 3. The Examiner questions how "more than one of R^1 or R^3 is a group of formula II, when applicants indicate that at least one of R^1 or R^3 is a pyrimidine." *Id.*

Definiteness under 35 U.S.C. § 112, second paragraph is determined from the point of view of one of ordinary skill in the art. M.P.E.P. § 2173.02. ("[T]he examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope."). Applicants respectfully submit that one of ordinary skill in the art would appreciate that radicals encompassed by formula II are not mutually exclusive from pyrimidines. As stated above, R¹ and/or R³ can be both a group of formula II and a pyrimidine. Applicants provide some examples of compounds that fall within the elected invention:

Example 1. R^1 is a pyrimidine of any formula and R^3 is a non-pyrimidine of formula II. (see, e.g., proviso of claim 2). Here, only one of R^1 and R^3 is a pyrimidine and only one of R^1 and R^3 is a group of formula II.

Example 2. R¹ is a pyrimidine but not of formula II and R³ is a pyrimidine of formula II. Here, both of R¹ and R³ are pyrimidines and only one of R¹ and R³ is a group of formula II.

Example 3. R¹ is a pyrimidine of formula II and R³ is a pyrimidine of formula II. Here, both of R¹ and R³ are pyrimidines and both of R¹ and R³ are groups of formula II.

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The claimed invention does not cover the scenarios where neither R¹ and R³ is a pyrimidine or neither R¹ and R³ is a group of formula II.

Applicants respectfully submit that the claim as presented in the previous response to the office action is sufficiently clear. Nevertheless, claim 1 has been amended in accordance with the Examiner's second suggested amendment at p. 4. Claim 1, as amended, defines R¹ and R³ as being chosen from the same list of substituents as for R², R⁴, and R⁵. The provisos remain unamended.

Accordingly, Applicants respectfully request withdrawal of this rejection.

IV. <u>Conclusion</u>

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner believes a telephone conference would be useful in resolving any outstanding issues, he is invited to call the undersigned at (617) 452-1621.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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